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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,928	01/21/2005	Ajay S Bhatnagar	ON/4 - 32602A	6202

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EXAMINER	
JAVANMARD, SAHAR	
ART UNIT	**PAPER NUMBER**
1609	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,928	BHATNAGAR ET AL.	
	Examiner	Art Unit	
	SAHAR JAVANMARD	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 9-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 9-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11 January 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Office Action is in response to the 371 of PCT/EP03/08377 filed January 21, 2005. Amended claims 1-3 and 9-25 are being examined on the merits herein.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 and 3 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the treatment of all diseases or conditions which respond to aromatase inhibition. The scope is unknown. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification does not provide sufficient information that all diseases or conditions which respond to aromatase inhibition are treatable by the administration of a bisphosphonate and an aromatase inhibitor as described in the methods claimed.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue

experimentation. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method of treating a patient with a bisphosphonate and an aromatase inhibitor for the treatment of all diseases or conditions which respond to aromatase inhibition. The nature of the invention is complex in that it encompasses the treatment of all proliferative diseases, including all types of cancers, as one example.

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass the treatment of all diseases or conditions which respond to aromatase inhibition by the administration of a bisphosphonate and an aromatase inhibitor to treat all diseases or conditions which respond to aromatase inhibition.

(3). Guidance of the Specification:

There is no guidance in the specification as to the list of diseases intended to be treated by the inhibition of the aromatase protein.

(4). Working Examples:

Applicant provides an *in vitro* example of intravenous administration of zoledronic acid and letrozole in the treatment of bone loss as measured by the total BMD. Applicant does not provide any pharmacological assays (*in vitro* or *in vivo*) for the treatment of all diseases or conditions which respond to aromatase inhibition by the administration of a bisphosphonate and an aromatase inhibitor.

(5). State of the Art:

While the state of the art is relatively high with regard to treating specific cancers, the state of the art with regard to treating cancer, generally, is underdeveloped. In particular, there is no known anticancer agent that is effective against all cancers. Carter, et al. (Chemotherapy of Cancer, 2nd ed., 1981) clearly teaches that for the forty known anticancer agents, none are effective against all cancers (pages 362-365). There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. This is true in part because cancers arise from a wide variety of

sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Even those that affect a single organ are often not generally treatable. For example, the main types of lung cancer are small cell (oat cell), giant cell, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, and mesothelioma. There is no such thing as a treatment of these generally because of their diversity. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

(6). Predictability of the Art:

The invention is directed to a method of treating a patient with a bisphosphonate and an aromatase inhibitor for the treatment of all diseases or conditions which respond to aromatase inhibition including proliferative diseases, i.e., cancer. It is well established that "the scope of enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). Cancers are especially unpredictable due to their complex nature. Please refer to the discussion of Carter, et al. and the state of

the art in (5) that shows the different treatments of cancers. The treatment of one type of cancer could not be necessarily the same for the other type.

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of skill in the art would have to first envision a combination of an appropriate pharmaceutical carrier, a dosage for each compound, the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for one of the claimed compounds. One would then need to test the combination in the model system to determine whether or not the combination is effective for inhibiting cancer cells. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding treatment of cancer with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. If again unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding treatment of cancer with any compound, the entire, unpredictable process would have to be repeated until successful. In order to practice Applicant's invention, it would be necessary for one to conduct the preceding experimentation for each type of cancer because, as described by Carter, et al., there is no known drug effective for inhibiting all types of cancer. Therefore, it would require undue, unpredictable

experimentation to practice the claimed invention to inhibit cancer cells in a mammal by administration of one of the compounds within the claims. *Genentech, Inc. v. Novo Nordisk*, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atentprotection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, a method of treating a patient with a bisphosphonate and an aromatase inhibitor for the treatment of all diseases or conditions which respond to aromatase inhibition including proliferative diseases, like cancer, is not considered to be enabled by the instant specification.

Claims 18-25 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the treatment of bone loss in patients suffering from an estrogen dependent disorder, does not reasonably provide enablement for the prevention of bone loss as recited in these claims.

The instant claims are drawn to a pharmaceutical composition and a method for the prevention of bone loss. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a

disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The instant invention pertains to a method for the prevention of bone loss.

The state of the prior art:

The skilled artisan would view that the prevention of one or more symptoms of bone loss totally, absolutely, or permanently, is highly unlikely, since one cannot guarantee that bone loss will always be prevented.

The relative skill of those in the art:

The relative skill of those in the art is very high.

The predictability or lack thereof in the art:

The skilled artisan would view that the treatment to prevent bone loss, absolutely, or permanently is highly unpredictable.

The amount of direction or guidance presented and the presence or absence of working examples:

In the instant case, no working examples are presented in the specification as filed showing how to prevent bone loss totally, absolutely, or permanently. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

Genentech, Inc. v. Novo Nordisk, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, e.g., the amount of direction or guidance provided, absence of working examples, and the predictability of the art discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test the combination in the instant claims whether preventing bone loss totally, absolutely, or permanently.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

There is no standard list of diseases treated with the inhibition of aromatase. It is unknown which diseases are intended to be treated.

The term, "effective amount", in the instant claims is a relative term that renders the claim indefinite. The term "effective amount" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear how much of the active ingredient in question is to be administered in order to treat a patient suffering from a disease or condition which responds to aromatase inhibitors.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 9-11, 12, 14-16, 18-20, 24 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Freyer et al. (European Journal of Internal Medicine, 2000).

Freyer discloses a study whereby patients with bone marrow involvement (BMI), common in metastatic breast cancer, and panycytopenia are administered a combination regimen including hormone therapy (i.e., anti-estrogens, LH-RH agonists, aromatase inhibitors (anastrozole), and progestin derivatives), repeated low dose chemotherapy, and bisphosphonates (pamidronate) (page 329-330, Introduction).

Freyer further teaches that among the five patients treated, three of them were post-menopausal with bone metastasis having ER+ and/or PR+ receptors (page 330, table 1).

Note that the instructions in claims 9 and 10 carry no patentable weight, thus these claims are also met by Freyer.

Thus Freyer anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 9-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freyer et al. in view of Reid (N. Engl. J. Med., 2002) and Iqbal (Expert Opin. Pharmacother.).

Freyer is discussed above. Freyer teaches anastrozole as the aromatase inhibitor and pamidronate as the bisphosphonate (page 331, see Treatment Strategy).

Freyer does not teach specifically teach zoledronic acid as the bisphosphonate or letrozole as the aromatase inhibitor. Additionally, Freyer does not teach that the bisphosphonate is administered once every six months.

Reid teaches administering in zoledronic acid to postmenopausal women with low bone density (title). Reid further teaches that zoledronic acid is the most

potent bisphosphonate that has been studied in clinical trials to date. Reid further teaches that zoledronic acid is superior to pamidronate in the treatment of cancer-related hypercalcemia. Additionally, Reid teaches that because of its high potency, only small doses are required for the inhibition of bone resorption, and long dosing intervals may be used (page 654, lines 1-6), including administering zoledronic acid at base line and again at six months (page 654, see Treamtent).

Iqbal teaches that aromatase inhibitors have been found effective in treating breast cancer in postmenopausal women (page 977, lines 11-13). Iqbal further teaches among other aromatase inhibitors, anastrazole and letrozole are markedly effective in inhibiting in situ aromatase activity (page 976, see 2.1.1.1 Endrocrine effects; page 977 Table 1). Additionally, Iqbal teaches that anastrazole and letrozole have both been approved by the FDA as first-line agents for the treatment of advanced breast cancer.

Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to have to have combined the methods of treatment as taught by Freyer, using specifically zoledronic acid as the bisphosphonate and letrozole as the aromatase inhibitor as taught by Iqbal because it is common practice among one of ordinary skill in the art to select the one of the most active analogs in a family of drugs to achieve the most promising results.

Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freyer et al. in view of Remington's: The Science and Practice of Pharmacy, Nineteenth Edition, Vol I, 1985, page 806). *In re* Ngai (70 USPQ2d

1862 (CA FC 2004)).

Freyer is discussed above.

Remington teaches that the inclusion of a package insert including "indications and use" of the pharmaceutical composition is mandated by 21 CFR 201.57. The addition of printed matter in the form of instructions for use in no way depends on the kit and the kit does not effect the pharmaceutical composition. All that the printed material does is teach new use for an existing product. Where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability. *In re* Ngai (70 USPQ2d 1862 (CA FC 2004).

Thus, it would have been obvious to one of ordinary skill in the art to have combined the aromatase inhibitor and bisphosphonate as taught by Freyer and included the medication as a package with instructions. The motivation is that it is mandated by law (21 CFR 201.57).

Conclusion

Claims 1-3 and 9-25 are not allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY STUCKER can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

JEFFREY STUCKER
SUPERVISORY PATENT EXAMINER